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Elements toward novel therapeutic targeting of the adrenergic system

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ABSTRACT

Adrenergic receptors belong to the family of the G protein coupled receptors that represent important targets in the modern pharmacotherapies. Studies on different physiological and pathophysiological properties of the adrenergic system have led to novel evidences and theories that suggest novel possible targeting of such system in a variety of pathologies and disorders, even beyond the classical known therapeutic possibilities. Herein, those advances have been illustrated with selected concepts and different examples. Furthermore, we illustrated the applications and the therapeutic implications that such findings and advances might have in the contexts of experimental pharmacology, therapeutics and clinic. We hope that the content of this work will guide researches devoted to the adrenergic aspects that combine neurosciences with pharmacology.

Contents

Abbreviations: NA, noradrenaline; a-AR, alpha adrenergic receptor; a1-AR, alpha adrenergic receptor; a1A-AR, alpha 1 A adrenergic receptor; a2-AR, alpha 2 adrenergic receptor; a 2A-AR, alpha 2 A adrenergic receptor; β-AR, beta adrenergic receptor; β1-AR, beta 1 adrenergic receptor; β2-AR, beta 2 adrenergic receptor; β2a-AR, beta 2 a adrenergic receptor; β3-AR, beta 3 adrenergic receptor; AD, Alzheimer's disease; PD, Parkinson's disease; GPCR, G protein coupled receptors; CNS, central nervous system; LC, locus coeruleus.

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1. Introduction

G protein coupled receptors (GPCRs) are of crucial importance in modern pharmacotherapies and neurosciences, a fact explained by the high amount of functions, diseases and disorders that involve GPCRs or their linked pathways including enzymes, second messengers (Barreda-Gómez et al., 2005, 2014; Duttlinger et al., 2003; Ghanemi and Hu, 2014; Hibert et al., 1994; Hofmann et al., 2013; Lin et al., 2011; Moser and Klose, 1993; Shen et al., 2013; Tofighi et al., 2012; Wirz et al., 2005) which, all, constitute potential targets in pharmacology and also in experimental biology to modify, stimulate or inhibit the signal transduction with or without the receptors activation. Therefore, investigating the properties of the GPCRs will without doubt lead to more advances towards clinical applications. Classified among GPCRs, adrenergic receptors constitute promising pharmacological targets. By "Adrenergic system" we refer to the adrenergic receptors, adrenaline, noradrenaline, in addition to the enzymes and messengers of the pathways related to the signal transduction after the receptors bind to the adrenaline, noradrenalin or a pharmakon. Herein, we briefly illustrate some concepts on how to go from the description of the physiological properties and the pathophysiological roles that have been described by recent publications to a variety of pharmacologic implications and therapeutic applications via applying those new concepts toward finding out new treatments. Importantly, data related to the physiological and pathological implication of the adrenergic receptors supported by structural analytic approaches (Leioatts et al., 2014; Nguyen et al., 2014; Weichert et al., 2014; Zhu et al., 2014) will lead to the definition of new compounds (candidates) for the drug screening. Indeed, the adrenergic receptors structures has similarities with the other GPCRs (Shukla et al., 2014) which make extrapolating some data from some other GPCR, such as pharmacogenetics (Thompson et al., 2014) and signal transmission (Zalewska et al., 2014), a source of details about the structures of the receptors. Furthermore, compounds deriving from the chemical synthesis constitute strong elements toward further pharmakon development.

2. Overview of the central adrenergic system

The adrenergic system, due to the diverse roles it plays in neurophysiology, represents a very important part of the nervous system. Thus, the neuropharmacology of the adrenergic system is promising. The two adrenergic neurotransmitters, adrenaline and noradrenaline (NA), act on both subtypes α (alpha) adrenergic receptor (a-AR) and β (beta) adrenergic receptor (β-AR) and govern a variety of functions (Bylund, 2013). Indeed, whereas both neurotransmitters regulate cell differentiation in the developing brain (Berger-Sweeney and Hohmann, 1997; Lauder, 1993; Lidow and Rakic, 1995; Lipton and Kater, 1989), NA is involved in developmental processes (Felten et al., 1982; Parnavelas and Blue, 1982; Sanders et al., 2008) and nervous system development regulation (Landis, 1990; Lauder, 1993; Lipton and Kater, 1989; Whitaker-Azmitia, 1991) particularly in the cortex (Blue and Parnavelas, 1982; Loeb et al., 1987; Maeda et al., 1974; Wendlandt et al., 1977). More importantly, NA directs a2-AR development (Landis, 1990; Lauder, 1993; Lipton and Kater, 1989; Whitaker-Azmitia, 1991) which confirms adrenergic receptors' (ARs) involvement in brain development (Blue and Parnavelas, 1982; Rowe et al., 1993; Soto-Moyano et al., 1994). Additionally, a2A-ARs were linked to neuronal differentiation, growth and neurotrophy of the developing brain (Bylund, 1988). Furthermore, a2A-ARs involve Protein kinase A (Chadzinska et al., 2012a) that regulates microtubule-associated protein 2 (MAP2) which mediates dendrite growth of cortical neurons (Song et al., 2004). Also, a2-ARs play an important role in the maturation of dendritic spines within the medial prefrontal cortex (mPFC) (Ren et al., 2012). In addition to evidences concerning the age-related differences, novel a2-AR properties became know. a2-AR expression periods within the white matter show the role of a2-AR in brain development. Indeed, after a2-ARs are highly expressed in the developing brain of rat they disappear in adulthood (Sanders et al., 2005). Further neurotrophic properties have also been attributed to β2-ARs. β2-ARs activation by clenbuterol is among the properties than could be exploited in further drug development. This results, in the rat brain, in the synthesis of three growth factors; nerve growth factors (NGF), basic fibroblast growth factor (bFGF) and transforming growth factor-beta 1 (TGF-b1) (Culmsee et al., 1999; Follesa and Mocchetti, 1993). Therefore, support the important role the adrenergic system plays during brain development indicated also by other publications and thus, such elements highlight the possible pharmacological exploitation of such properties in neurodegenerative diseases treatment. Indeed, numerous publications have indicated that for neuropathologic disorders including AD, PD, epilepsy, brain trauma and stroke, therapies aiming to enhance the synthesis of endogenous growth factors could provide novel therapeutic arsenals to treat such disorders (Carswell, 1993; Semkova and Krieglstein, 1999), especially that agents that interact with β-AR are interesting including propranolol, a non-specific β-ARs antagonist that could prevent some memory impairment (Debiec and Ledoux, 2004; Ferry and McGaugh, 2000), whereas β-ARs agonists constitute cognitive enhancing molecules (Ferry and McGaugh, 1999; Friedman et al., 1999; Gibbs and Summers, 2000; LaLumiere et al., 2003; Zarrindast et al., 2004) and regulators of both amyloid and neurotrophin production (Counts and Mufson, 2010) indicating further the role elements targeting the adrenergic system might have in memory loss that is seen in some neurodegenerative diseases.

The wide distribution of a2-ARs within the central nervous system (CNS) (Nicholas et al., 1993; Unnerstall et al., 1984; Wamsley et al., 1992) indicates the physiological importance they have in different brain regions. The cognitive functions constitute illustrative examples. Learning and memory have been linked to dendritic spine morphology (Kasai et al., 2003; Ren et al., 2012) and transplantation of norepinephrine neurons into aged rats improved certain types of learning paradigms (Collier et al., 1988). In addition, the prefrontal cortex (PFC) is linked to both behavior-related neurophysiology (Goldman-Rakic, 1996) and cognitive functions (Avery et al., 2000; Ramos and Arnsten, 2007). Furthermore, several papers have shown that improving memory and other cognitive functions can be obtained via a2-ARs stimulation in some species (Arnsten and Cai, 1993; Brennan and Arnsten, 2008; Franowicz et al., 2002; Ramos et al., 2006; Wang et al., 2007) including humans (Jakala et al., 1999). Moreover, a2-ARs appear to play a role in emotional memory (de Quervain et al., 2007). Importantly, within the amygdala and hippocampus, β-ARs have been linked to memory function processes (Bush et al., 2010; Gibbs and Summers, 2005; Murchison et al., 2011). Indeed, β-ARs are implicated in emotional memory (Cahill et al., 1996) and learning process (Roullet and Sara, 1998; Rutecki, 1995; Sternberg et al., 1985). β-AR expression in the hippocampus is well documented (Hillman et al., 2005). Furthermore, noradrenergic signaling through a1-AR has also been linked to behavioral effects (Smiałowska et al., 1994) and also prefrontal cortical function regulation (Ramos and Arnsten, 2007) which further illustrates a1-AR's implication in cognition and the possibility of its targeting in disease in which loss of cognitive functions is observed such as AD (Ghanemi, 2014a; Mufson et al., 2005).

On the other hand, ARs have been linked to some metabolic and cellular processes including glycogen formation, oxidative metabolism (stimulation of a2-ARs), glutamate uptake (a1-ARs stimulation), glycogenolysis and increased Na+, K+ ATPase activity (β- ARs activation) (Hertz et al., 2010). NA has also been shown to have anti-inflammatory properties (Dello Russo et al., 2004; Feinstein et al., 2002) which might turn out to be beneficial if therapeutically

exploited. Herein, the cardioprotective property of the a1A-ARs (Shi et al., 2013) is worth mentioning. Importantly, since the β2-ARs pathway is a biased signaling (Zheng et al., 2013) with multiple signaling regulatory proteins (Nygaard et al., 2013), a considerable number of molecules and effectors could be future pharmacological targets in divers diseases and disorders.

2.1. Pathophysiological highlights

In addition to the above illustrated adrenergic-related functions, pathogenetic studies have provided further orientations for developing drugs that target the adrenergic system which led to clinical implications (Hurt and Angelotti, 2007; Koshimizu et al., 2007; Michelotti et al., 2000) or applications such as in the contexts of heart failure (Bristow et al., 1990), eye disease (Schwartz et al., 2005), oncology (Ramondetta et al., 2013), anesthetic practice (Salonen et al., 1992), immunology (Fan and Wang, 2009; Sanders, 2006) and geriatric medicine (Schutzer and Mader, 2003). For instance, in both drug addiction and Parkinson's disease (PD), dysregulation of striatal NA signaling is implicated (Aston-Jones and Kalivas, 2008; Fornai et al., 2007; Rommelfanger and Weinshenker, 2007; Sofuoglu and Sewell, 2009; Weinshenker and Schroeder, 2007) which is relevant since adrenergic receptors are highly expressed in the striatum (Hara et al., 2010; Nicholas et al., 1993; Paschalis et al., 2009; Pisani et al., 2003; Rommelfanger et al., 2009). Thus, publications have shown the possible neuroprotective role of NA that may contribute to striatal control of motor functions (Marien et al., 2004; Rommelfanger and Weinshenker, 2007) showing another aspect of NA and adrenergic receptors within the striatum that might lead to the development of novel therapeutic approaches in PD.

Also within the context of neurological disorders, abnormalities of the adrenergic systems of astrocytes are probably involved in the pathogenesis of multiple sclerosis, inflammation, malfunction in Alzheimer's disease (AD) and mood disturbances in affective disorders (Hertz et al., 2004). In other brain regions, NA has been involved in the pathological phenomena of post-traumatic stress disorder (Krystal and Neumeister, 2009) and AD (Weinshenker, 2008). Indeed, NA depletion in AD contributes to the neuroinflammation that participates in the aggravation of AD (Cullen et al., 1997; Ghanemi, 2014b; Lambert et al., 1998; Vitolo et al., 2002; Walsh et al., 2002; Wang et al., 2004). In addition, we observe a cytokine expression enhancement in the microglia, which is also caused by reduction of NA (Heneka et al., 2002) thus, contributing more to the inflammatory component of AD. Moreover, the impaired memory in aged Alzheimer's patients is linked with degeneration of the noradrenergic system as well (Leslie et al., 1985; Mann and Yates, 1986; Stemmelin et al., 2000), therefore, supporting theories indicating the importance of the adrenergic system in cognitive functions and presents NA as an anti-inflammatory agent. Importantly, a recent paper suggested that in both ischemia and neuro-diseases that include inflammatory components within their pathogenesis, neuroprotective effects could be obtained via the regulation of catecholamine level as a therapeutic approach (Markus et al., 2010).

The pharmacological implications derive not only from physiological and pathological processes in which adrenergic system is implicated, but also from the fact that the activity of adrenergic system can affect other systems or other brain structures, especially if we consider the brain as a complex network within which neurotransmitters interact continuously (Ghanemi, 2013b). However, as the adrenergic system-related pharmacology enlarges, the related toxicology becomes noticeable as well. As illustrated, both α2-autoreceptors and heteroreceptors can influence the medial prefrontal cortical acetylcholine release (Tellez et al., 1999) and targeting astrocytes with noradrenergic drugs will also affect the neurons, as they interact with astrocytes within neurochemical networks (Hertz et al., 2004). These neural network implications also highlight the importance of maintaining vigilant monitoring of drugs targeting such a system.

3. From pathological mechanisms to therapeutic implications

Resulting from research based on pathophysiological descriptions, many drugs targeting the adrenergic systems are either in use or under investigation. For instance, clonidine, an a2-AR agonist, is used as an anti-hypertensive agent that acts on cardiovascular regulatory centers in the brainstem (Yamazato et al., 2001). In psychiatry, other a2-AR agonists are used as antidepressants (Davis et al., 2001) including mirtazapine which is an a2-AR, 5 HT2 and 5-HT3 serotoninergic receptors' agonist (Sanders et al., 2011) used to treat social phobia (Mrakotsky et al., 2008) and to improve cognitive functions (Arnsten et al., 1996; Franowicz and Arnsten, 1999; Franowicz et al., 2002). Guanfacine, an a2A-AR selective agonist, has been used to treat patients suffering from attention deficit hyperactivity disorder (ADHD) (Sallee et al., 2009) and other psychiatric disorders (Faraone and Glatt, 2010; Sallee and Eaton, 2010; Taylor and Russo, 2001). Clozapine and risperidone, which are two antipsychotics, have affinities to a2-AR (Bymaster et al., 1996). Importantly, atomoxetine, a selective NA reuptake inhibitor is effective in treating patients with ADHD (Garnock-Jones and Keating, 2009) via enhancing synaptic norepinephrine that stimulates a2-AR in PFC as suggested by Arnsten (2009). On the other hand, tricyclic antidepressants have been reported to involve a2-AR signaling within their pharmacodynamics (Zhang et al., 2009). Moreover, in the hippocampus, isoproterenol (a β-AR agonist) can, via activating β-ARs, promote the model of learning and the long-term potentiation (LTP) in cornu ammonis 1 (CA1) pyramidal cells (Lin et al., 2003; Moody et al., 1998; Thomas et al., 1996). These examples illustrate the importance targeting the adrenergic system has in psychiatry. Regarding insomnia, that might be related to psychiatry, and because the implications of a2-ARs in the regulation of sleep–wake processes (Ramesh et al., 1995) and as NA are implicated in both sleep-related processes and pathologies (Mitchell and Weinshenker, 2010), we suggest the possible targeting of a2-ARs in cases like insomnia. Furthermore, β-ARs agonists might be beneficial in diseases with neuronal excitability alteration including epilepsy (Rutecki, 1995) and long-term potentiation (LTP) modulation (Hillman et al., 2005). This is due to the fact that it has been shown that neuronal excitability can be enhanced via cerebral β-ARs activation (Mueller and Dunwiddie, 1983; Stoop et al., 2000), whereas β-ARs antagonists may be given as a therapeutic option in cases of anxiety and stress related disorders to reduce some of the side effects (Abraham et al., 2008).

Hypoxic-ischemic brain injury-related phenomena include oxygen-free radical formation, the release of both glutamate and catecholamines (including noradrenaline), in addition to the elevation of intracellular calcium (Ma et al., 2004). Because both glutamate release and calcium changes in addition to some cell damage in ischemia (ex: hippocampal neurons) are influenced by α2-receptors, cerebroprotective properties are attributed to a2-ARs agonists (Bickler and Hansen, 1996) thus, dexmedetomidine, which has sedative (Tobias and Berkenbosch, 2002) and analgesic properties (Ma et al., 2004) have also been shown to reduce infarct size in models of brain ischemia (Jolkkonen et al., 1999; Matsumoto et al., 1993). Dexmedetomidine is considered as a neuroprotective agent that activates the α2A adrenergic receptor subtype *in vitro* and *in vivo* models of hypoxic-ischemic injury probably via attenuating the massive release of catecholamines (Ma et al., 2004).

For the neurodegenerative diseases, agents that act on β-ARs may be with benefits in AD as well. In fact, β2-ARs activation prevents the Beta-amyloid (Aβ) inhibition of LTP (Wang et al., 2009a). Furthermore, during the progression of AD, noradrenergic signaling has been shown to mediate neuroprotective properties, and we may also

target brain-derived neurotrophic factor (BDNF) delivery (Nagahara et al., 2009) or alternatively, use NA replacement therapy (Weinshenker, 2008) to obtain the same neuroprotective effect. Importantly, a genetic study has indicated that the combination of G protein β 3 subunit (GNB3) and β1-AR gene polymorphisms results in susceptibility to AD. They also have suggested the regulation of cerebral adrenergic receptors as a new pharmacological addition to AD therapies (Bullido et al., 2004). Moreover, it has been shown that in neonates, activators of both β1-ARs and β2-ARs represent potential neuro-protective agents (Markus et al., 2010), whereas others have indicated that co-treatment combining both β2-ARs agonists and β1-ARs antagonists may increase the cerebroprotective properties of β2-ARs agonists *in vivo* (Junker et al., 2002). In addition to previous studies that have highlighted noradrenergic system's neuroprotective properties (Chen et al., 2007; Heneka et al., 2002; Madrigal et al., 2007; Traver et al., 2005; Troadec et al., 2001), β1-ARs stimulation results in the translation of striatal enriched protein tyrosine phosphatase (Buchel et al., 2012), which exists in several brain structures. This has been linked to the learning process (Hu et al., 2007) again expanding the neuropharmacological area of targeting the adrenergic system.

Targeting astrocytic adrenoceptors, which might constitute a promising therapeutic approach for several pathologies that have been shown to involve astrocyte-related pathophysiological pathways (Meitzen et al., 2011) including PD, AIDS-related dementia and prion diseases (Hertz et al., 2004), represent another example among the many perspectives that can be cited within this context. Importantly, the neurotrophic properties attributed to the noradrenergic system may also be applied *in vivo* as a neural growth factor leading to the possibility of promoting the maturation and development of the prefrontal cortical structure and function by the use of α-2A agonist that could be specifically delivered into the PFC of human infants (Ren et al., 2012) or *in vitro* in cell cultures, for example to enhance receptor expression which may provide better conditions for their study. In this context, molecules, such as laboratory reagents and solvents that have pharmacological or biological actions on receptor expression or cell properties, also constitute useful agents either to create new laboratory conditions or even to provide starting points to develop new therapeutic agents (Ghanemi, 2013a, 2014e).

4. Emerging pharmacological potentials

In addition to the previously described therapeutic applications, advances in research on divers have indicated the huge unexploited pharmacological potential of the adrenergic system. For instance, a-ARs antagonists have represented the mainstay of therapy of lower urinary tract symptoms (Miller, 2013) and a2-AR agonists, that are considered as antihypertensive agents and as sedative analgesics (Madden et al., 2013), might be effective during excessive fever by attenuating the lethal elevations in body temperature (Madden et al., 2013). Herein, we further review more recent advances.

4.1. Central adrenergic receptors as an emerging target for depression and anxiety

Links between central adrenergic systems and neuropsychiatric disorders have been established. Indeed, papers are describing links between the psychological aspects and both the neurotransmitters and the elements belonging to the adrenergic system. For instance, whereas NA deficiency was reported in severe depression (Callado et al., 1998; Ordway et al., 1994), two publications have indicated that suicide victims have a high density of both a2-ARs and a2-AR-A mRNA (De Paermentier et al., 1997; Escriba et al., 2004). In addition, genetically polymorphisms in the a2-AR-A gene may be linked to suicide predisposition (Fukutake et al., 2008). On the other hand, patients suffering from attention deficit hyperactivity disorder (ADHD) and some other neuropsychiatric disorders commonly show deficits in PFC functions (Brennan and Arnsten, 2008; Casey et al., 1997). Many neuropsychiatric diseases are related to the loss or malformation of dendritic spine (Calabrese et al., 2006) and new evidence show the benefits targeting some adrenergic receptors may have in cases of depression (Erdogan, 2010) (such as the drug Mirtazapine (Kasper et al., 1997)) and anxiety. Indeed, whereas the deficiencies of serotonergic system are believed to be involved in anxiety and depression (Consoli et al., 2007) a decreased central dopaminergic and/or noradrenergic transmission is likely involved in the pathology of depression (Guiard et al., 2008) which not only puts more light on the bridges linking neural imbalances and psychiatric disorders but also indicate potential therapies . Furthermore, a recent study that used substance P receptor antagonists, a putative new class of antidepressant/anxiolytic drugs, suggested that tachykinin NK1 receptor antagonists interfere with serotoninergic system via noradrenaline neurons (Haddjeri and Blier, 2008). These elements are supported by previous data describing improvement of depression-like behavior in rats (Yang et al., 2014). In addition, the noradrenergic system has been implicated in depressive disorder (Overstreet et al., 2008) which further indicates how for the treatment of stress-related disorders, adrenoceptors may represent a therapeutic target (Tamburella et al., 2010) which is worth exploring. Such data raise the importance of the adrenergic system within the therapies of psychiatric disorders and encourage more investigations. For instance, β3-ARs and a-ARs of the locus coeruleus (LC) constitute putative targets for diseases, including depression and anxiety.

4.1.1. Beta 3 adrenergic receptors

After β1-ARs and β2-ARs have been shown to be involved in depressive disorders (Overstreet et al., 2008), investigations have focused on the role β3-ARs might play in the context of depression. They indicated that the activation of β3-ARs could turn out to become a new therapy for anxiety and depressive disorders (Stemmelin et al., 2008).

To elucidate some of the pharmacological properties of the β3-ARs, that do not exist only in the brain (Imbrogno et al., 2006; Morimoto et al., 2004; Sahi et al., 2012) and governs divers functions including some metabolic pathways (Sahi et al., 2012), we describe amibegron. Amibegron or SR58611A, which is the first selective β3-ARs agonist described with antidepressant (Tanyeri et al., 2013b) and anxiolytic (Tanyeri et al., 2013a) properties in rodents, has been used in studies that have raised the importance of β3-AR as a target for treatment of depression (Claustre et al., 2008; Tanyeri et al., 2013b). Herein, two important facts have to be mentioned; first, β3 adrenergic chronic signaling during social stress represents an adaptive response (Chuang et al., 2010) and secondly, the study about the antidepressant-like effects of the amibegron, was coherent with the hypothesis that β3-AR might constitute a target for the pharmacotherapy of stress-related disorders (Tamburella et al., 2010). More importantly, the antidepressant property of amibegron has been proven in an animal model of depression (Overstreet et al., 2008). In addition, as amibegron is orally active and brain-penetrant (Stemmelin et al., 2008), this may facilitate drug development and improve cerebral bioavailability. On the other hand, β3-AR gene Trp64Arg polymorphism has been linked to obesity, type 2 diabetes and cardiovascular disease, and since the incidence of these three disorders is increased in major depression and schizophrenia, we suggest a relationship between β3-AR and both major depression and schizophrenia (Sasayama et al., 2012) which further raised the potential pharmacotherapeutic importance of β3- AR.

The interaction of β 3-ARs activity with other neurotransmissions which has been shown to play important roles in depression

and anxiety, has further strengthened the previously described theories. In fact, the activation of the β3-AR has been suggested to increase brain serotonin synthesis (Consoli et al., 2007) whereas amibegron anxiolytic- and antidepressant-like activities might be mediated, at least in part, via the increase of brain serotonergic and noradrenergic neurotransmissions (Claustre et al., 2008). Finally, it was proposed that neuronal production can be increased via the activation of both neurogenic precursors and stem cells through β3-ARs and points out a new therapeutic target for novel antidepressants (Jhaveri et al., 2010). Since such concepts might lead to the development of a new generation of antidepressants, further investigations are not only encouraged but required especially that β3-ARs might also be a target for other diseases, including portal hypertension (Vasina et al., 2012), in addition to the facts that new elements related to both β3-ARs pathways (Zhang et al., 2012) and structure (Sahi et al., 2012) are being revealed.

4.1.2. Locus coeruleus alpha adrenoceptors

Links between depression and the α-adrenergic system of the locus coeruleus (LC) made targeting these receptors a new area of research in neuropharmacology. Indeed, whereas depression may be a result of excessive LC activity (Stone et al., 2009), studies support the theory that antidepressant drugs decrease the activity of the LC (West et al., 2009).

In the LC, which is considered as a stress-responsive region (Stone et al., 2011) a 2-ARs autoregulate norepinephrine (NE) neurons (Guiard et al., 2008). However, a 1-ARs are highly expressed in LC as well (Stone et al., 2009), which indicates the implication of a-ARs in the mechanism of depression. In fact, correlations between noradrenergic system and both the etiopathogenesis and recovery from depression have been established (Miguelez et al., 2011). Furthermore, it has been shown that the antidepressant effects of noradrenaline reuptake inhibitors (NaRIs) and serotonin reuptake inhibitors (SSRIs) might be improved by the co-administration of selective a2-AR antagonists. This could be explained by cerebral enhancing of extracellular NA concentrations (Ortega et al., 2010). Moreover, targeting a2-ARs for treating both negative/cognitive symptoms in schizophrenia and related psychiatric disorders constitutes a therapeutic opportunity (Masana et al., 2011).

Recent studies have indicated the existence of correlations between LC adrenoreceptors and depression. For instance, the interaction of noradrenaline with a2-ARs plays a role in the inhibition of LC neurons *in vivo* by fluoxetine, a selective serotonin reuptake inhibitor (Miguelez et al., 2009). Moreover, 6-fluoronorepinephrine (6FNE), a selective a-ARs agonist (Stone et al., 2011) that elicits a rapid and effective antidepressant and anti-stress response (Stone et al., 2011), was reported to possess antidepressant actions (Stone et al., 2011). 6FNE is also hypothesized to strongly stimulate the a 1-ARs of the mouse's LC, thus inhibits the tonic or stress-induced activity of the LC (Stone et al., 2009). Importantly, researchers have also indicated that 6FNE is likely to inhibit neural activity in LC (Stone et al., 2011).

These evidences introduce the LC ARs as new targets to treat depression. In addition, as noradrenergic LC is implicated in other functions such as the ascending and descending pain pathways (Alba-Delgado et al., 2012), we suppose a possible use of LC α-adrenergic receptors' ligands for other therapeutic purposes, on the one hand. On the other hand, targeting LC α-adrenergic receptors will have numerous side effects. Thus, deeper research remains required to reach a new and efficient therapeutic approach.

4.2. Adrenergic system between nervous and immune systems: new potentials?

In keeping a state of homeostasis, the interactions between the nervous, endocrine and immune systems represent the key element of the body response against different stimuli (Ader et al., 1995). The adrenergic system has important roles in the neuroimmunology-related processes. Indeed, a number of neurotransmitters and hormones have their receptors on some immune cells (Chadzinska et al., 2012b). The immune response of divers is regulated via the CNS (Dantzer et al., 2008). In addition, skin, oral and gut mucosae, the peritoneum and lungs, which are implicated in the immune response, are innervated (Nance and Sanders, 2007) which illustrates the existence of strong neuro-immune interactions.

Many different pathways have been linked to adrenaline receptors. For instance, whereas a1-ARs act via protein kinase C (PKC) activation with both phospholipase C (PLC) (de Smet et al., 2011) and inositol 1,4,5-triphosphate (IP3) as second messengers (Lafontan and Berlan, 1993; Myslivecek et al., 2008), a 2-ARs reduce intracellular cyclic adenosine monophosphate (cAMP) through adenylyl cyclase (Ac) activation (Myslivecek et al., 2008). Both a-AR and β-AR subtypes have been shown to be expressed on mammalian innate immune cells (Nance and Sanders, 2007). Several studies have focused on the adrenergic regulation of immunologic mechanisms. Furthermore, the β2a-ARs probably modulate the immune response in fish (Nickerson et al., 2001; Wang et al., 2009b) whereas, in mammals, adrenaline inhibits oxygen radical formation via β2-ARs-related pathways (Barnett et al., 1997; Weiss et al., 1996). Adrenaline, NA and β-ARs agonists inhibit the processes of synthesis and secretion of pro-inflammatory cytokines (Elenkov et al., 2000; Hasko et al., 1998; Szelenyi et al., 2000). In contrast, they stimulate the liberation of anti-inflammatory interleukin-10 (IL-10) (Suberville et al., 1996; van der Poll et al., 1996; Van der Poll and Lowry, 1997). It has also been shown that β-AR agonists can suppress the synthesis of interferon-gamma (IFN- γ) by T helper cells 1(Th1) (Borger et al., 1998; Ramer-Quinn et al., 1997). Moreover, antibody secretion at early stages of the adaptive response can be suppressed by catecholamines (Flory, 1990). In addition, adrenaline and isoproterenol (a β-AR agonist) are able to reduce reactive oxygen species (ROS) synthesis in rainbow trout pronephric phagocytes (Flory and Bayne, 1991). More importantly, a recent publication (Chadzinska et al., 2012b) explained that ARs and adrenaline are linked with the regulation of the innate immune response in common carp (Cyprinus carpio L.). The same publication added that adrenaline inhibits both CXC ligands and the expression of their receptors. Furthermore, it has also shown that, with cortisol and opioid ligands (Chadzinska et al., 2009a, 2009b, 2012b) the adrenergic system also plays a role in the process of down regulation of the immune system. The adrenergic system is also implicated in modulation of the inflammatory responses that are mediated by neuroendocrine factors, stress hormones (cortisol, catecholamines) and opioids (Chadzinska et al., 2012b).

These publications illustrate some aspects of the interactions between the three main systems engaged in maintaining endogenous homeostasis (nervous, endocrine and immune systems). Therefore, we suggest that the effects of a drug used to regulate any of these three systems will have effects on the two other, because of the complexity and inter-influences of the endogenous ligands involved in the interaction between these three systems. In addition, of the explanations those papers give about the cellular and molecular properties of GPCRs, data also show that catecholamines play roles in regulating some immune functions and inflammatory processes.

For instance, within the central nervous system noradrenaline elicits anti-inflammatory effects and plays a neuroprotective function (McNamee et al., 2010). Thus, such elements might constitute starting points to develop agents that, via interacting with catecholamines-related systems (receptors or the intracellular enzymes of the related pathways), could reduce or even inhibit the immune response or the inflammatory phenomenon. Such drugs

might be very important in diseases with inflammatory component or auto-immune diseases. More important, the ability of adrenaline to inhibit oxygen radical formation via β2-ARs suggests that β2-ARs agonists could be beneficial to prevent or treat ischemic accident or reduce the impact of some oxygen radicals on cell degenerative-diseases via a cell protective role. These results merit further investigation to find out whether or not such properties can be therapeutically useful in neurodegenerative disease.

4.3. Adrenergic systems, novel properties and not only in the central nervous system: the example of beta adrenergic ligands and cell growth

In addition to controlling the neurophysiological phenomena, some neurotransmitters have been linked to cell growth-related pathways that involve GPCRs. Indeed, the autonomic nervous system has been shown to innervate salivary gland tissues. Both parasympathetic and sympathetic nerves regulate salivary gland function and development as well (Yeh et al., 2012). Since 1960s isoproterenol (a non-selective agonist for the G-protein coupled β-AR) has been suggested to play a role in salivary gland development (Selye et al., 1961). At that period, two papers described the potential of isoproterenol to induce salivary gland enlargement (Borsanyi and Blanchard, 1962; Selye et al., 1961). This growth mechanism was shown to implicate several molecular and enzymatic processes. In fact, repeated isoproterenol injections enhance mitogen activated protein kinase (MAPK) and progressive activation of epidermal growth factor receptor (EGFR) transactivation pathways (Purushotham et al., 1992, 1993, 1994; Wang et al., 1993). In addition, more recent publications (Yeh et al., 2003, 2005) showed that, in the salivary HSY cell line, isoproterenol stimulates extracellular-signal regulated kinase 1 and 2 (ERK1/2) phosphorylation. Later, Yeh et al. (2012) have reported that nuclear factor kappa B (NF-κB) and cAMP response element bind protein (CREB) constitute, with the mitogen activated protein kinase (MAPK) pathway, key effectors in the growth response to isoproterenol.

Such new concepts relating isoproterenol effects to salivary gland growth via molecular pathways can open new doors for advances about β-AR. More importantly, it can lead to development of novel methods in bioengineering of salivary gland repair, replacement or regrowth (Baum, 2000) to treat salivary dysfunction, such as those observed after radiation therapy for head and neck cancer, or prevent oral disease and regain physiological secretory functions (Yeh et al., 2012) via β-ARs agonists that stimulate salivary gland cells growth. Thus β-ARs agonists can be regarded as "growth factors".

In addition to presenting new evidences about the molecular and the enzymatic basis of GPCRs functions, such data will help to further understand the biological effects of ligands on the DNA transcription processes. Therefore, reach therapeutic aims through stimulating or selected DNA regions via membrane receptors' agonists or antagonists. Furthermore, and as the growth process involves several molecular and enzymatic process, such molecules and enzymes could also be targeted to modify their pathways, rather than targeting the receptors.

On the other hand, the possibility of stimulating cell growth may provide new chemical agents which could be used in cell cultures to stimulate cell growth and thus facilitate studies in a shorter period of time, via modifying the growth speed. Importantly, and *in vivo,* such properties could be helpful to develop bioengineering synthetic tissues for organs replacement. In contrast, we might target the receptors, or the molecules implicated in the growth pathway, to inhibit cell growth in some cases, like salivary glands cancer, thus obtain a new generation of anticancer drugs.

5. Pharmacovigilance and perspectives

As adrenergic receptors affect the function of other systems as the cardiovascular system, therapies targeting adrenergic receptors may result in side effects (Faizi et al., 2011). For instance, β-ARs agonists induce tachycardia and other arrhythmias (Friedman et al., 1999). Thus, drugs targeting ARs will not only require a higher pharmacovigilance, but these side effects will also limit the use of such agents. In addition, due to the possible influences of the adrenergic system on non-adrenergic neural system, we should also consider the resulting aspects in the related pharmacovigilance. Furthermore, the existence of several receptor subtypes makes the drug selectivity very important when targeting the adrenergic system against a multitude of neurological and psychiatric diseases via modulating noradrenergic receptor activity or down-stream signaling or both of them (Hertz et al., 2004).

Herein, other aspects of the pharmacovigilance can be also illustrated, for instance a recent study has indicated that for agents targeting a2-AR, age-related differences in clinical response exist (Sanders et al., 2011). These new elements are consistent with the previous related data which show that tricyclic antidepressants, monoamine oxidase inhibitors, and venlafaxine, that exert their clinical effects mainly by acting on the noradrenergic system (Subhash et al., 2003), may not be recommended to treat depression in children, whereas they are efficacious in adults (Geller et al., 1999; Hazell et al., 2000; Varley, 2003; Whittington et al., 2004). Furthermore, in 2007 the immature regulatory system for the a2-AR was proposed as one of the reasons that may explain the reduced effect of tricyclic antidepressant in pediatric populations compared with adults (Bylund and Reed, 2007; Deupree et al., 2007). On the other hand, long term consequences of the drugs acting on a2-AR require clinicians to pay more attention to children and adolescent populations if such populations are treated with such agents (Sanders et al., 2008) because of the age-related differences.

The previous elements show some of the main therapeutic possibilities that targeting adrenergic system may provide, including treatment of neurodegenerative diseases, ischemic pathologies, psychiatric diseases (Hertz et al., 2004) and pathologies that include inflammatory phenomena within their pathogenesis, in addition to withdrawal from addictive drugs and cognitive disorders. Other usage remains possible, especially with the implication of the adrenergic system in other pathologies such as the Parkinson's disease (Ghanemi, 2013c). Moreover, targeting the intracellular pathways remain therapeutic possibilities as well (Ghanemi, 2013d) which may provide more possibilities for the related diseases especially with the development of fields including pharmacology (Ghanemi, 2014d; Ghanemi and Hu, 2014) and pharmacognosy (Boubertakh et al., 2013; Dhami, 2013; Ghanemi, 2014c, 2014f).

The different physiological functions which the adrenergic system governs, the diverse pathological processes and disorders it is implicated in, and the existent similarities between the majority of the GPCRs (to which adrenergic receptors belong), dictate that further studies will surely lead to the identification of new targets and also elucidate some pathogenetic mechanisms. This will help to develop new drugs based on the properties of the receptors and the factors that may affect their functions (Ghanemi et al., 2013), especially with the high number of chemical and natural compounds that could be active against adrenergic receptors, in addition to the use of the novel technologies and methods.

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